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TOXICOLOGICAL HIGHLIGHT

Cardiovascular Toxicity of Inhaled Ambient Particulate Matter

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The article highlighted in this issue is "Oil Fly Ash-Induced Elevation of Plasma Fibrinogen Levels in Rats," by Sarah Y. Gardner, James R. Lehmann, and Daniel L. Costa (pp. 175–180).

The key unanswered question in the particulate matter (PM)-related health concern is the biological plausibility of the association between PM and the observed adverse cardiopulmonary health effects. These adverse health outcomes have been demonstrated by both cross-sectional and time-series epidemiological studies. Key to the validity of the biological plausibility is the need to identify the component(s) of airborne PM responsible for adverse effects as well as the populations at risk. The plausibility of the association between PM and increases in morbidity and mortality has been strongly questioned because the adverse cardiopulmonary effects have been observed at very low PM concentrations, often below the current NAAQS for PM10. Researchers have even suggested that there appears to be no concentration threshold for these effects.

Most importantly, adverse cardiovascular outcomes have been demonstrated at ambient PM concentrations which apparently do not produce experimental pulmonary inflammation or injury in healthy individuals or test animals. Logic, as well as epidemiological evidence, suggests that such small inhaled PM concentrations may be more likely to affect a sensitive subpopulation with compromised health. In fact, controlled studies using healthy animals exposed to concentrated ambient PM have not demonstrated effects that are likely to lead to life-threatening consequences in healthy individuals (Table 1). Studies by Gordon and colleagues have observed a limited number of small increases in heart rate and no pulmonary effects in normal and compromised animals after a single exposure to inhaled concentrated ambient PM at concentrations as high as 919 $\mu g/m^3$ (Gordon *et al*., 2000). Likewise, Godleski's animal studies have observed adverse outcomes only in dogs and rats with compromised health exposed to inhaled concentrated ambient PM (Godleski *et al*., 2000).

Epidemiological studies have begun to explore the issue of sensitive subpopulations. Initial findings are consistent with the observations from the 1952 and 1962 London episodes, which found that pollution-associated mortality is age-dependent, with the elderly being the most susceptible. PM-associated changes in heart rate or heart rate variability have been reported in panel studies by 3 groups of investigators (Peters *et al*., 2000; Pope *et al*., 1999; Liao *et al*., 1999). Pope reported results from a panel study of 90 elderly subjects in Utah Valley, an area that has periodic episodes of increased PM during the winter. A small (5–10 beats/min) increase in daily heart rate was found to be significantly associated with increased PM levels on the previous 1–5 days. Heart rate response to PM was similar in healthy subjects and in subjects with chronic cardiac or respiratory disease. Peters reanalyzed heart rate data from the MONICA study, an epidemiological study of randomly selected adults aged 25–64 in southern Germany. Analysis of data from over 2500 adults indicated that the pollution episode was associated with a small, but statistically significant increase (2–3 beats/min) in daily heart rate. The association of increased heart rate and PM was not affected by adjustment for weather, age, or cardiovascular risk factors. In a similar fashion, Liao and colleagues have demonstrated that heart rate variability changes in residents of a retirement home were consistently associated with daily PM levels.

The study by Gardner and colleagues in this issue of *Toxicological Sciences* (pp. 175–180) has determined that an inflammatory dose of residual oil fly ash (ROFA) delivered by intratracheal instillation produces an increase in plasma fibrinogen in healthy rats. Because fibrinogen is a known risk factor for ischemic heart disease and stroke, the authors suggest that this alteration in the coagulation pathway could take part in the triggering of cardiovascular events in susceptible individuals. Such reasoning is consistent with the epidemiology studies that have demonstrated an association between episodic exposure to PM and increased cardiovascular morbidity and mortality in elderly people. These data are supported by Peters and colleagues, who have demonstrated that plasma viscosity changes are associated with ambient PM concentrations.

Abundant evidence suggests the route of administration affects the outcome in inhalation toxicology studies. Logically,

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TABLE 1
Experimental Evidence for the Biologic Plausibility of the Cardiovascular Effects Associated with Ambient PM Exposure

	Strength of evidence[a]	
Factor	Human studies	Animal studies
Coagulation pathways	Weak	Weak
Neural		
Heart rate variability	Moderate	Moderate
Heart rate change	Moderate	Weak
Airway irritation	None	None
Arrhythmia	Weak	Moderate
Biological agents[b]	Weak	Moderate
Susceptible individuals	Strong	Moderate
Inflammatory mediators	None	Weak

[a]The strength of evidence is based upon empirical evidence from human or animal studies in which inhaled ambient PM or relevant concentrations of surrogate particles were used.
[b]Moderate *in vitro* evidence.

healthy animals and humans are unlikely to have a life-threatening response to relevant concentrations of inhaled ambient urban PM. Animal studies using the intratracheal route of administration, however, have clearly shown that ambient particles can produce life-threatening effects at high doses, particularly in animal models of cardiopulmonary disease. While the relevance of this route of administration is often called into question, studies using intratracheal instillation of ambient or surrogate combustion particles have contributed important information regarding the relative toxicity of particles from different sources. Although the instillation route of exposure somewhat tempers their significance, these instillation studies clearly show that some particle types, particularly those with high metal sulfate content, have far greater toxicity than other types. Thus, the ability of investigators to efficiently test the relative toxicological strength of PM components is the strength of tracheal instillation studies.

Another conclusion that can be drawn from the Gardner study is that elevations in plasma fibrinogen were observed in healthy rats only at the highest treatment dose. Because the lower treatment doses are known to cause pulmonary injury and inflammation, albeit to a lower extent, the absence of plasma fibrinogen changes at these lower doses suggests that only acute administration at high dose levels are able to produce a cardiovascular effect in healthy test animals. Whereas pulmonary injury and inflammation have not been observed in healthy animals or human volunteers exposed to concentrated ambient PM, it is therefore uncertain whether the present study directly addresses the events leading to life-threatening cardiovascular events in some individuals during PM pollution episodes. Thus, as noted by the authors, only limited evidence exists to provide a viable link between the ambient PM-induced changes in plasma viscosity observed in epidemiology studies with any analogous coagulation pathway response in test animals. It should be noted, however, that the role of increased fibrinogen in cardiac outcomes may not be limited to its role in the coagulation pathways. Fibrinogen is also thought to have antioxidant properties and to act as an acute phase protein.

In addition to an alteration in the coagulation pathway as demonstrated in the study by Gardner, other pathways have been suggested which link inhaled PM with cardiovascular events. These proposed pathways focus on the role of neural pathways in the control of the cardiovascular system. As with the plasma viscosity hypothesis, however, the alterations in neural control of the cardiopulmonary system that result from exposure to relevant concentrations of ambient urban PM are quite small and within the range of normal inter-person variability. How these small changes can account for the increased cardiac events associated with exposure to PM is unclear. For example, the observed changes in heart rate in panel studies are typically less than 5 heart beats/min. Such a change is equivalent to that which may occur when an individual changes from a seated resting position to an upright walking position. Similarly, the changes in heart rate variability that have been reported in healthy human subjects exposed to concentrated ambient PM are relatively small. It has been suggested that such changes may be significant in terms of their health effects for two reasons. First, while small changes are unlikely to have an important effect on homeostasis in healthy individuals, they could have a greater effect in individuals with preexisting cardiopulmonary disease. Second, whereas it may be unlikely for researchers to observe a life-threatening event in a small sample size, such as is used in animal toxicology and clinical studies, a small clinical change in neural control of the cardiovascular system could be important in a small proportion of a large population of individuals. This latter fact is the major strength of epidemiology studies, which can demonstrate associations but not causality. Thus, the firm identification of the precise physiological mechanism(s) linking PM exposure with cardiac events may be extremely difficult in animal and clinical studies, unless the proper model of cardiopulmonary disease is used. Therefore, if one accepts the hypothesis that healthy individuals are not at cardiovascular risk from exposure to relevant concentrations of ambient PM, the greatest challenge in PM health research is to identify the sensitive subpopulation(s).

Taken together, animal and human studies indicate that increased levels of ambient outdoor PM can cause small increases in heart rate, heart rate variability, and blood coagulation factors in normal or compromised individuals, and that this effect is unlikely to be caused by confounders such as co-pollutants or weather conditions. Yet the question remains: Are these small increases in heart rate biologically relevant and how could these changes possibly relate to mortality? As discussed above, there are a number of possible mechanistic pathways that could lead to serious cardiac events as a result of

exposure to ambient urban PM at concentrations that do not evoke pulmonary injury.

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